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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,484	CONTRERAS ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-90,92-95,97-107 and 109-112* is/are pending in the application.

4a) Of the above claim(s) *74-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90, 92-95, 97-107 and 109-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/27/2010 has been entered.

Claims 74-90, 92-95, 97-107, 109-112 are pending in the present application.

Claims 74-89 were withdrawn previously from further consideration because they are directed to an invention nonelected with traverse in the reply filed on 8/9/06.

Accordingly amended claims 90, 92-95, 97-107 and 109-112 are examined on the merits herein.

Terminal Disclaimer

The terminal disclaimer filed on 9/27/2010 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent No 7,252,933; US Patent No. 7,507,573 and US Patent No. 6,803,225 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Amendment

The rejections on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 7,252,933; US Patent No.

7,507,573 and US Patent No. 6,803,225 were withdrawn in light of the the terminal disclaimer filed on 9/27/2010.

Claim Objections

Claim 90 is objected to because of the term "mannosyl transferase" which should be a single word "mannosyltransferase".

Claim 107 are objected to because of the phrase "the sole Golgi mannosyl transferase**s** genetic disruption" is grammatically incorrect and that the term 'mannosyl transferases" should be a single word. The above phrase should be replaced with - - the sole Golgi mannosyltransferase genetic disruption - - to obviate this objection.

Enablement

Amended claims 90, 92-95, 97-107 and 109-112 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A genetically engineered strain of *Pichia*, wherein said strain is transformed with **a nucleic acid coding for a full-length *T. reesei* α-1,2-mannosidase**, wherein said *T. reesei* α-1,2-mannosidase is genetically engineered to contain an ER-retention signal and the genomic Och1 gene in said strain is disrupted such that said strain fails to produce a functional Och1 protein and the Och1 gene disruption is the sole Golgi mannosyltransferase genetic disruption in said strain, and wherein as a result of expression of said *T. reesei* α-1,2-mannosidase said strain produces $Man_5GlcNAc_2$ as a predominant N-glycan structure or a predominant intermediate N-glycan structrure; a kit

comprising the same strain and a method of reducing the glycosylation of an endogenous glycoprotein and/or a heterologous glycoprotein expressed in the same genetically engineered *Pichia* strain;

does not reasonably provide enablement for **a genetically engineered strain of *Pichia* transformed with other nucleic acid coding for a *T. reesei* α-1,2-mannosidase to attain the specific desired result, a kit and a method of using the same strain as broadly claimed**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. ***The rejection is slightly modified.***

The present disclosure is not enabled for the instant broadly claimed invention for the reasons discussed below.

1. The breadth of the claims

The instant claims are directed to a genetically engineered strain of *Pichia* transformed with **a nucleic acid coding for a *T. reesei* α-1,2-mannosidase (including but not necessarily limited to a full length *T. reesei* α-1,2-mannosidase)**, wherein the genomic OCH1 gene is said strain is disrupted and **as a result of the expression of said *T. reesei* α-1,2-mannosidase, the genetically engineered strain produces $Man_5GlcNAc_2$ as a predominant N-glycan structure or a predominant intermediate N-glycan structure**; a kit comprising the same strain and a method of reducing glycosylation of an endogenous glycoprotein and/or a heterologous glycoprotein using the same strain.

2. The state and the unpredictability of the prior art

At about the effective filing date of the present application (6/30/2000), little was known about a modification of the protein glycosylation pathway in a *Pichia* yeast strain to generate Man5GlcNAc2 as a predominant N-glycan structure or a predominant intermediate N-glycan structure as evidenced at least by the teachings of Martinet et al (Biotechnology Letters 20:1171-1177, 1998; IDS) and Callewaert et al. (FEBS Letters 503:173-178, 2001). In contrast, there are several known double and triple mutants of *Saccharomyces cerevisiae* that have been characterized to produce $Man_5GlcNAc_2$ and/or $Man_8GlcNAc_2$ as a predominant glycoform species (Nakanishi-Shindo et al, J. Biol. Chem. 268:26338-26346, 1993; IDS; and Chiba et al, J. Biol. Chem. 41:26298-26304, 1998; IDS). Additionally, *T. reesei* α-1,2-mannosidase was overexpressed in a *pichia pastoris* strain, however the expression and/or activity of *T. reesei* α-1,2-mannosidase was not sufficient to generate $Man_5GlcNAc_2$ as the predominant glycoform species (see Martinet et al and Callewaert et al references cited above). Several years after the effective filing date of the present application, Choi et al (PNAS 100:5022-5027, 2003) disclose that **a proper length of the α-1,2-mannosidase catalytic domain is one of several factors that determine the yield of $Man_5GlcNAc_2$ in *P. pastoris* Och1 mutant strains** (see at least page 5026, col. 1, second full paragraph). Moreover, as is well recognized in the art any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. There is a high degree of unpredictability associated with the use of the claimed embodiment as evidenced by the teachings of

Rudinger in discussing peptide hormones. Rudinger stated that "The significance of particular amino acids and sequences for different aspects of biological activity (for this instance the enzymatic activities of α-1,2-mannosidase or glucosidase II) can not be predicted a priori but must be determined from case to case by painstaking experimental study (Page 6, first sentence of Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976; IDS). Furthermore, it should be further emphasized that the relationship between the sequence of a peptide and its tertiary structure associated for its activity is not well understood and is not predictable (Ngo et al., *In* Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994; IDS). Since the prior art at the effective filing date of the present application does not provide any guidance regarding to the aforementioned issues, it is incumbent upon the instant specification to do so. Furthermore, the physiological art is also recognized as unpredictable (MPEP 2164.03).

3. The amount of direction or guidance provided

Apart from disclosing the use of **an expression vector encoding the full-length *T. reesei* α-1,2-mannosidase** for transforming a *Pichia pastroris* strain whose genomic OCH1 gene is disrupted to attain a predominant N-glycan structure or a predominant intermediate N-glycan structure (see at least examples 2-3 and Figures 6-7 and 10), the instant specification fails to provide sufficient guidance (exemplification is part of a guidance) for a skilled artisan on how to make and use any other encoded *T. reesei* α-1,2-mannosidase **(e.g., less than a full-length or a fragment or functional part of a *T. reesei* α-1,2-mannosidase)** for producing Man5GlcNAc2 as a predominant N-glycan

structure or a predominant intermediate N-glycan structure. In addition to a high degree of unpredictability associated with the make and/or use of an enzyme fragment having a specific desired property as discussed above, it should be noted that **full-length *T. reesei* α-1,2-mannosidase has a pH optimum of 5.0 while most enzymes active in the ER and Golgi apparatus of yeasts have pH optima that are between 6,5 and 7.5** (Gerngross, US 2002/0137134, IDS; see at least paragraph 68), it is unclear whether any *T. reesei* α-1,2-mannosidase that is less than an a full-length enzyme or a functional fragment of the *T. reesei* α-1,2-mannosidase would still be stable and still sufficient active in the less than optimal environment of a yeast's ER to yield Man5GlcNAc2 as a predominant N-glycan structure or a predominant intermediate N-glycan structure. As already noted above, several years after the effective filing date of the present application, Choi et al (PNAS 100:5022-5027, 2003) disclose that **a proper length of the α-1,2-mannosidase catalytic domain is one of several factors that determine the yield of $Man_5GlcNAc_2$ in *P. pastoris* Och1 mutant strains** (see at least page 5026, col. 1, second full paragraph).

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the state and the

unpredictability of the relevant art, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed on 9/27/2010 (page 8) has been fully considered but it is respectfully not found persuasive for the reason discussed below.

Applicants argue basically that by deleting the claim language referring to "an enzymatically active fragment" of said *T. reesei* α-1,2-mannosidase in currently amended claims, the rejection under 35 U.S.C 112, first paragraph, is rendered moot.

Please note that the limitation "a nucleic acid coding for a *T. reesei* α-1,2-mannosidase" **includes but not necessarily limited to a nucleic acid coding for a full length *T. reesei* α-1,2-mannosidase**, Please refer to the above slightly modified rejection as well as the indicated scope of enablement set forth in the Office action mailed on 5/26/2010 (page 4).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/

Primary Examiner, Art Unit 1633